NIOSH Skin Notation Profiles

Isophorone Diisocyanate

SK

ID^{SK}

[SK]

SYS

SYS (FATAL

DIR

DIR (IRR)

DIR (COR)

SEN

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

NIOSH Skin Notation (SK) Profiles

Isophorone Diisocyanate
[CAS No. 4098-71-9]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

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Foreword

As the largest organ of the body, the skin performs multiple critical functions, such as serving as the primary barrier to the external environment. For this reason, the skin is often exposed to potentially hazardous agents, including chemicals, which may contribute to the onset of a spectrum of adverse health effects ranging from localized damage (e.g., irritant contact dermatitis and corrosion) to induction of immune-mediated responses (e.g., allergic contact dermatitis and pulmonary responses), or systemic toxicity (e.g., neurotoxicity and hepatoxicity). Understanding the hazards related to skin contact with chemicals is a critical component of modern occupational safety and health programs.

In 2009, the National Institute for Occupational Safety and Health (NIOSH) published *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009-147]. This document provides the scientific rationale and framework for the assignment of multiple hazard-specific skin notations (SK) that clearly distinguish between the systemic effects, direct (localized) effects, and immune-mediated responses caused by skin contact with chemicals. The key step within assignment of the hazard-specific SK is the determination of the hazard potential of the substance, or its potential for causing adverse health effects as a result of skin exposure. This determination entails a health hazard identification process that involves use of the following:

- Scientific data on the physicochemical properties of a chemical
- Data on human exposures and health effects
- Empirical data from *in vivo* and *in vitro* laboratory testing
- Computational techniques, including predictive algorithms and mathematical models that describe a selected process (e.g., skin permeation) by means of analytical or numerical methods.

This *Skin Notation Profile* provides the SK assignments and supportive data for isophorone diisocyanate (IPDI). In particular, this document evaluates and summarizes the literature describing the hazard potential of the substance and its assessment according to the scientific rationale and framework outlined in CIB 61. In meeting this objective, this *Skin Notation Profile* intends to inform the audience—mostly occupational health practitioners, researchers, policy- and decision-makers, employers, and workers in potentially hazardous workplaces—so that improved risk-management practices may be developed to better protect workers from the risks of skin contact with the chemicals interest.

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Contents

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
CIB	Current Intelligence Bulletin
cm^2	square centimeter(s)
cm/hour	centimeter(s) per hour
DEREK	Deductive Estimation of Risk from Existing Knowledge
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
EC	European Commission
FCAT	Freund's complete adjuvant
GHS	Globally Harmonized System for Classification and Labelling of Chemicals
GPMT	guinea pig maximization test
IARC	International Agency for Research on Cancer
IPDI	isophorone diisocyanate
(IRR)	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
k_{aq}	coefficient in the watery epidermal layer
k_p	skin permeation coefficient
k_{pol}	coefficient in the protein fraction of the stratum corneum
k_{psc}	permeation coefficient in the lipid fraction of the stratum corneum
LD_{50}	dose resulting in 50% mortality in the exposed population
LD_{Lo}	dermal lethal dose
LLNA	local lymph node assay
LOAEL	lowest-observed-adverse-effect level
log K_{OW}	base-10 logarithm of a substance's octanol–water partition
M	molarity
m^3	cubic meter(s)
MEST	mouse ear swelling test
mg	milligram(s)
mg/kg	milligram(s) per kilogram body weight
mg/m^3	milligram(s) per cubic meter
mL	milliliter(s)
mL/kg	milliliter(s) per kilogram body weight
mM	millimole(s)
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration

REL	recommended exposure limit
RF	retention factor
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SI ratio	ratio of skin dose to inhalation dose
SK	skin notation
S_W	solubility
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
USEPA	United States Environmental Protection Agency
µL	microliter(s)

Glossary

Absorption—The transport of a chemical from the outer surface of the skin into both the skin and systemic circulation (including penetration, permeation, and resorption).

Acute exposure—Contact with a chemical that occurs once or for only a short period of time.

Cancer—Any one of a group of diseases that occurs when cells in the body become abnormal and grow or multiply out of control.

Contaminant—A chemical that is (1) unintentionally present within a neat substance or mixture at a concentration less than 1.0% or (2) recognized as a potential carcinogen and present within a neat substance or mixture at a concentration less than 0.1%.

Cutaneous (or percutaneous)—Referring to the skin (or through the skin).

Dermal—Referring to the skin.

Dermal contact—Contact with (touching) the skin.

Direct effects—Localized, non-immune-mediated adverse health effects on the skin, including corrosion, primary irritation, changes in skin pigmentation, and reduction/disruption of the skin barrier integrity, occurring at or near the point of contact with chemicals.

Immune-mediated responses—Responses mediated by the immune system, including allergic responses.

Sensitization—A specific immune-mediated response that develops following exposure to a chemical, which, upon re-exposure, can lead to allergic contact dermatitis (ACD) or other immune-mediated diseases such as asthma, depending on the site and route of re-exposure.

Substance—A chemical.

Systemic effects—Systemic toxicity associated with skin absorption of chemicals after exposure of the skin.

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1 Introduction

1.1 General Substance Information:

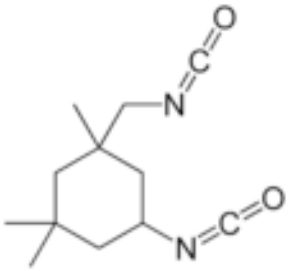
Chemical: Isophorone Diisocyanate

CAS No: 4098-71-9

Molecular weight (*MW*): 222.3

Molecular formula: $C_{12}H_{18}N_2O_2$

Structural formula:



Synonyms:

Isophorone diisocyanate; 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl-isocyanate; Isophorone diamine diisocyanate; IPDI

Uses:

Isophorone diisocyanate (IPDI) is primarily used as a chemical intermediate during the production of polyurethanes paints and varnishes [ACGIH 2001].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with IPDI and (2) the rationale behind the hazard-specific skin notation (SK) assignment for IPDI. The SK assignment is based on the scientific rationale and logic outlined in the *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009]. The summarized information and health hazard assessment are limited to an evaluation of the potential health effects of dermal exposure to IPDI. A literature search was conducted through May 2014 to identify information on IPDI, including but not limited to data relating to its toxicokinetics, acute toxicity, repeated-dose systemic toxicity, carcinogenicity, biological system/function–specific effects (including reproductive and developmental effects and immunotoxicity), irritation, and sensitization. Information was considered from studies of humans, animals, or appropriate modeling systems that are relevant to assessing the effects of dermal exposure to IPDI.

1.3 Overview of SK Assignment

IPDI is potentially capable of causing numerous adverse health effects following skin contact. A critical review of available data has resulted in the following SK assignment for IPDI: **SK: DIR (IRR)-SEN**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for IPDI.

2 Systemic Toxicity from Skin Exposure (SK: SYS)

No toxicokinetic studies following dermal exposure to IPDI in humans or animals were identified. No reports of death or other systemic toxicity following dermal absorption

Table 1. Summary of the SK assignment for IPDI

Skin notation	Critical effect	Data available
SK: DIR (IRR)	Skin irritation	Sufficient animal data
SK: SEN	Skin allergy	Sufficient human and animal data

were identified in humans. Acute dermal toxicity studies identified also are inconclusive with regard to the potential of IPDI to be acutely toxic. Bello et al. [2008a] found polymeric IPDI was detectable in 89% of people wearing gloves (most typically latex gloves) during spraying with a maximum value of 12.2 nanograms polymeric IPDI that was collected under gloves. In another study, Bello et al. [2008b] applied 30 microliters (µL) of isocyanates diluted in ethyl acetate over an area of 5 square centimeters (cm^2) to guinea pig skin. The results indicated that the polymer form of IPDI remained on the skin longer than methyl diisocyanate [Bello 2008]. The potential of IPDI to pose a skin absorption hazard was also evaluated, with use of a predictive algorithm for estimating and evaluating the health hazards of dermal exposure to substances [NIOSH 2009]. The evaluation method compares an estimated dose accumulated in the body from skin absorption and an estimated dose from respiratory absorption associated with a reference occupational exposure limit. On the basis of this algorithm, a ratio of the skin dose to the inhalation dose (SI ratio) of 12.3 was calculated for IPDI. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, IPDI is considered to be absorbed through the skin following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No dermal lethal doses (LD_{Lo}s) of IPDI for humans have been identified. The dermal LD_{50} value (the dose resulting in 50% mortality in the exposed animals) was 4.52 milliliters per kilogram (mL/kg) [corresponding to 4800 mg/kg] in rabbits [Mellon Institute 1967]. IPDI was applied as a 50% solution to 2-3 cm^2 of the shaved abdomens and backs of rats, and an LD_{50} of 1 mL/kg [corresponding to 1062 mg/kg] was reported following 4 hours of exposure and an LD_{50} of 0.5 mL/kg [corresponding to 531 mg/kg] was reported follwing 7 days of exposure [Farbenfabriken Bayer AG 1968]. However, a report by Hüls A.G. [1989] reported an LD_{50} of greater than 7000 mg/kg in rats. Because the conflicting reports in rats and the high dermal LD_{50} value reported in rabbits is higher than the critical dermal LD_{50} value of 2000 mg/kg body weight that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009], IPDI is not considered acutely toxic following dermal exposure.

No epidemiological studies or case reports of systemic effects produced by dermal exposure were identified. No repeat-dose, sub-chronic, or chronic studies following dermal exposure to IPDI were identified in humans or animals. No standard toxicity or specialty studies evaluating biological system/function specific effects (including reproductive and developmental effects) following dermal exposure to IPDI were identified. No studies evaluating the carcinogenic potential dermal exposure to IPDI were identified. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for IPDI.

No toxicokinetic studies following dermal exposure to IPDI were identified. However, a predictive mathematical model (see Appendix) indicates that the chemical can be absorbed through the skin. Conflicting data in acute toxicity studies [Farbenfabriken Bayer AG 1968; Hüls A.G. 1989] and the lack of epidemiological studies in humans, repeat dose, sub-chronic, and chronic toxicity studies in animals precludes adequate evaluation

Table 2. Summary of the carcinogenic designations* for IPDI by numerous governmental and nongovernmental organizations

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2011]	No designation
US EPA [2014]	No designation
European Parliament [2008]	No designation
IARC [2012]	No designation
EC [2014]†	No designation
ACGIH [2001]	No designation

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; USEPA = United States Environmental Protection Agency.
*The listed cancer designations were based on data from nondermal (such as oral or inhalation) exposure rather than dermal exposure.
†Date accessed.

of the potential for IPDI to cause systemic health effects. Therefore, on the basis of the data for this assessment, IPDI is not assigned the SK: SYS notation.

3 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies for corrosivity of IPDI or *in vitro* tests for corrosivity using human skin models or *in vitro* tests of skin integrity using cadaver skin were identified. Evidence of the corrosivity of IPDI is limited to a single study involving a single rabbit in which 500 µL IPDI (99% pure) was corrosive when applied to 1 cm^2 of the skin under occlusion [Bayer AG Farbenfabriken Toxikologie 1994]. No studies evaluating the skin irritating potential of the substance were identified in humans. However, a limited number of animal studies were identified. Stem [1989] conducted a primary irritancy study using mice and concentrations of IPDI ranging from 0.1 to 30.0%. Following being shaved and abraded, the back was treated for 5 consecutive days with IPDI. The author reported that that 1.0% IPDI was the minimum concentration necessary to produce irritation in mice and that treatment with 3.0% IPDI resulted in an irritation response nearly twice as severe [Stern 1989]. Guinea pigs were topically administered 30–300 millimoles (mM) [corresponding to 6669–66690 mg] IPDI in olive oil in a volume of 30µL under gauze patch occlusion for 6 hours. Erythema was observed 24 hours post IPDI chemical application for the 100mM and 300 mM treatment groups [Bio/dynamics Inc. 1984]. The structure activity relationship model, Deductive Estimation of Risk from Existing Knowledge (*DEREK*), predicted IPDI to be negative for skin irritation.

Use of a single rabbit in the skin corrosivity study conducted by Bayer Corp. [1994] precludes adequate evaluation of the potential of IPDI to be corrosive to the skin of rabbits. However, data from the primary irritancy studies **[Bio/dynamics Inc. 1984; Stern 1989; Bayer AG Farbenfabriken Toxikologie 1994]*** sufficiently demonstrate that IPDI is a skin irritant. Therefore, on the basis of the data for this assessment, IPDI is assigned the SK: DIR (IRR) notation.

* References in bold text indicate studies that serve as the basis of the SK assignments.

4 Immune-mediated Responses (SK: SEN)

Skin sensitization induced by dermal exposure to IPDI has been well-documented in humans and animals. Over a period of 13 years, 345 people who were examined for suspected occupational skin diseases were tested for allergy to isocyanate monomers, and of these 9 had positive reactions to IPDI [Aalto-Korte et al. 2012]. IPDI was shown to provoke allergic dermatitis in four sensitized workers patch tested with 1% of the substance in ethanol [Lachapelle and Lachapelle-Ketelaer 1979]. Militello et al. [2004] described two sculptors who presented with allergic contact dermatitis, both of whom showed positive reactions when patch tested with 1% IPDI in petroleum. In another study, positive reactions were reported in 4 of 17 factory workers that presented with eczema and were patch tested with IPDI [Frick et al. 2003].

The potential of IPDI to elicit contact hypersensitivity was also assessed in animals. Zissu et al. [1998] reported a sensitization grade of IV in Buehler tests in guinea pigs administered 0.5 mL of 5% IPDI solution. In a study conducted by the Bio/dynamics Inc. [1984] IPDI exhibited the potential to produce dermal sensitization in guinea pigs. Ciba Geigy Limited [1984] conducted a challenge test in which two intradermal induction of 0.1 mL were followed by application of 0.4g of a 3% IPDI solution to the skin of guinea pigs in vaseline. The authors observed positive erythema and edema reactions in 95% of the animals. In a mouse ear swelling test (MEST) [NTP 1987; Stern et al 1989], female mice were sensitized dermally to either 0, 0.1%, 0.3%, or 1.0% solutions of IPDI daily for 5 consecutive days and challenged 7 days later with a 3.0% solution. Some mice received an additional intradermal injection of Freund's complete adjuvant (FCAT). Statistically significant hypersensitivity was observed in mice when administered a 1.0% sensitizing concentration and a challenge concentration of 3.0%, with or without pretreatment with FCAT [Stern et al. 1989]. Plitnick et al. [2005] used the ribonuclease protection assay (RPA) to detect increases in the Th2 cytokine mRNA and conducted murine local lymph node assays (LLNA) on IPDI and several other isocyanates. Mice exposed to IPDI had elevated Th2 cytokines indicating that IPDI could be a respiratory sensitizer, and results from the LLNA indicate that 2% IPDI provoked a stimulation index of 50 [Plitnick et al. 2005]. A substance with a stimulation index greater than or equal to 3 is considered a sensitizer [NIOSH 2009]. In a later study, Selgrade et al. [2006] conducted a LLNA and also reported that 2% IPDI provoked a stimulation index of 50, indicating IPDI is a skin sensitizer. A similar stimulation index was earlier reported in mice by Dearman et al. [1992a]. Skin sensitization was also seen in mice topically treated with 0.05 to 2.5% IPDI administered in acetone:olive oil (4:1, weight/volume basis) [Dearman et al. 1992b]. *DEREK* predicted IPDI to be a plausible skin sensitizer.

Based on positive responses from patch testing in humans **[Lachapelle and Lachapelle-Ketelaer 1979; Frick et al. 2003; Militello et al. 2004; Aalto-Korte et al. 2012]** and results from sensitization tests in guinea pigs **[Bio/dynamics Inc. 1984; Ciba Geigy Limited 1984]**, Buehler test **[Zissu et al. 1998]**, MEST **[NTP 1987; Stern et al 1989]** and LLNA **[Dearman et al. 1992a, 1992b; Plitnick et al. 2005; Selgrade et al. 2006]**, sufficient data exist to conclude that IPDI is a skin sensitizer in both humans and animals. Therefore, on the basis of the data for this assessment, IPDI is assigned the SK: SEN notation.

5 Summary

Toxicokinetic studies that evaluated the potential of IPDI to be absorbed through the skin following dermal exposure were not identified. However, predictions from a mathematical model indicate that IPDI has the potential to be absorbed through the skin (see Appendix). Conflicting data in acute toxicity studies [Farbenfabriken Bayer AG 1968; Hüls

Table 3. Summary of previous skin hazard designations for IPDI

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption
OSHA [2014]*	No designation
ACGIH [2001]	No designation
EC [2014]*	R38: Irritating to skin
	R43: May cause sensitization by skin contact

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.
*Date accessed.

A.G. 1989] and the lack of epidemiological studies in humans, repeat dose, sub-chronic, and chronic toxicity studies in animals precludes adequate evaluation of the potential for IPDI to cause systemic health effects. Skin irritation studies in rabbits and mice **[Bio/dynamics Inc. 1984; Stern 1989; Bayer AG Farbenfabriken Toxikologie 1994]** indicate that IPDI can be irritating to the skin. Positive responses from patch testing in humans **[Lachapelle and Lachapelle-Ketelaer 1979; Frick et al. 2003; Militello et al. 2004; Aalto-Korte et al. 2012]** and results from the Buehler test **[Zissu et al. 1998]**, MEST **[NTP 1987; Stern et al 1989]** and LLNA **[Dearman et al. 1992a, 1992b; Plitnick et al. 2005; Selgrade et al. 2006]**, provide sufficient evidence that IPDI has the potential to cause sensitization of the skin. Therefore, on the basis of these assessments, IPDI is assigned a composite skin notation of **SK: DIR (IRR)-SEN**.

Table 3 summarizes the skin hazard designations for IPDI previously issued by NIOSH and other organizations. The equivalent dermal designations for IPDI, according to the Global Harmonization System (GHS) of Classification and Labelling of Chemicals, are Skin Irritation Category 2 (Hazard statement: Causes skin irritation) and Skin Sensitization Category 1 (Hazard statement: May cause an allergic skin reaction) [European Parliament 2008].

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Note: Asterisks (*) denote sources cited in text; daggers (†) denote additional resources.

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Appendix: Calculation of the SI Ratio for IPDI

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for IPDI. Although the SI ratio is considered in the determination of a substance's hazard potential following skin contact, it is intended only to serve as supportive data during the assignment of the NIOSH SK. An in-depth discussion on the rationale and calculation of the SI ratio can be found in Appendix B of the *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009].

Overview

The SI ratio is a predictive algorithm for estimating and evaluating the health hazards of skin exposure to substances. The algorithm is designed to evaluate the potential for a substance to penetrate the skin and induce systemic toxicity [NIOSH 2009]. The goals for incorporating this algorithm into the proposed strategy for assigning SYS notation are as follows:

1. Provide an alternative method to evaluate substances for which no clinical reports or animal toxicity studies exist or for which empirical data are insufficient to determine systemic effects.
2. Use the algorithm evaluation results to determine whether a substance poses a skin absorption hazard and should be labeled with the SYS notation.

The algorithm evaluation includes three steps:

1. determining a skin permeation coefficient (k_p) for the substance of interest,
2. estimating substance uptake by the skin and respiratory absorption routes, and
3. evaluating whether the substance poses a skin exposure hazard.

The algorithm is flexible in the data requirement and can operate entirely on the basis of the physicochemical properties of a substance and the relevant exposure parameters. Thus, the algorithm is independent of the need for biologic data. Alternatively, it can function with both the physicochemical properties and the experimentally determined permeation coefficient when such data are available and appropriate for use.

The first step in the evaluation is to determine the k_p for the substance to describe the transdermal penetration rate of the substance [NIOSH 2009]. The k_p, which represents the overall diffusion of the substance through the stratum corneum and into the blood capillaries of the dermis, is estimated from the compound's molecular weight (MW) and base-10 logarithm of its octanol–water partition coefficient (log K_{OW}). In this example, k_p is determined for a substance with use of Equation 1. A self-consistent set of units must be used, such as outlined in Table A1. Other model-based estimates of k_p may also be used [NIOSH 2009].

Equation 1: Calculation of Skin Permeation Coefficient (k_p)

$$k_p = \frac{1}{\frac{1}{k_{psc} + k_{pol}} + \frac{1}{k_q}}$$

where k_{psc} is the permeation coefficient in the lipid fraction of the stratum corneum, kpol is the coefficient in the protein fraction of the stratum corneum, and kaq is the coefficient in the watery epidermal layer. These components are individually estimated by

$$\log k_{psc} = -1.326 + 0.6097 \times \log K_{ow} - 0.1786 \times MW^{0.5}$$

$$k_{pol} = 0.0001519 \times MW^{-0.5}$$

$$k_{aq} = 2.5 \times MW^{-0.5}$$

The second step is to calculate the biologic mass uptake of the substance from skin absorption (skin dose) and inhalation (inhalation

dose) during the same period of exposure. The skin dose is calculated as a mathematical product of the k_p, the water solubility (S_W) of the substance, the exposed skin surface area, and the duration of exposure. Its units are milligrams (mg). Assume that the skin exposure continues for 8 hours to unprotected skin on the palms of both hands (a surface area of 360 cm^2).

Equation 2: Determination of Skin Dose

Skin dose

$$= k_p \times S_w \times \text{Exposed skin surface area} \times \text{Exposure time}$$

$$= k_p(\text{cm/hour}) \times S_w\ (\text{mg/cm}^3) \times 360\ \text{cm}^2 \times 8\ \text{hours}$$

The inhalation dose (in mg) is derived on the basis of the occupational exposure limit (OEL) of the substance—if the OEL is developed to prevent the occurrence of systemic effects rather than sensory/irritant effects or direct effects on the respiratory tract. Assume a continuous exposure of 8 hours, an inhalation volume of 10 cubic meters (m^3) inhaled air in 8 hours, and a factor of 75% for retention of the airborne substance in the lungs during respiration (retention factor, or RF).

Equation 3: Determination of Inhalation Dose

Inhalation dose = OEL × Inhalation volume × RF

$$= \text{OEL}\ (\text{mg/m}^3) \times 10\ \text{m}^3 \times 0.75$$

The final step is to compare the calculated skin and inhalation doses and to present the result as a ratio of skin dose to inhalation dose (the SI ratio). This ratio quantitatively indicates (1) the significance of dermal absorption as a route of occupational exposure to the substance and (2) the contribution of dermal uptake to systemic toxicity. If a substance has an SI ratio greater than or equal to 0.1, it is considered a skin absorption hazard.

Calculation

Table A1 summarizes the data applied in the previously described equations to determine the SI ratio for IPDI. The calculated SI ratio was 12.3. On the basis of these results, IPDI is predicted to represent a skin absorption hazard.

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Table A1. Summary of data used to calculate the SI ratio for IPDI

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hr	8.077×10^{-2}
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hr	1.1019×10^{-5}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.1677
Molecular weight (MW)*	amu	222.29
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})*	None	4.75
Calculated skin permeation coefficient (k_p)	cm/hr	5.452×10^{-2}
Skin dose		
Water solubility (S_w)*	mg/cm^3	2.93×10^{-3}
Calculated skin permeation coefficient (k_p)	cm/hr	
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	0.4601
Inhalation dose		
Occupational exposure limit (OEL)†	mg/m^3	0.005
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	3.75×10^{-2}
Skin dose–to–inhalation dose (SI) ratio	None	12.3

*Variables identified from SRC [2009].
†The OEL used in calculation of the SI ratio for IPDI was the NIOSH recommended exposure limit (REL) [NIOSH 2005].

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